

Malignant pineal germ-cell tumors: An analysis of cases from three tumor registries

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The exact incidence of pineal germ-cell tumors is largely unknown. The tumors are rare, and the number of patients with these tumors, as reported in clinical series, has been limited. The goal of this study was to describe pineal germ-cell tumors in a large number of patients, using data from available brain tumor databases. Three different databases were used: Surveillance, Epidemiology, and End Results (SEER) database (1973–2001); Central Brain Tumor Registry of the United States (CBTRUS; 1997–2001); and National Cancer Data Base (NCDB; 1985–2003). Tumors were identified using the International Classification of Diseases for Oncology, third edition (ICD-O-3), site code C75.3, and categorized according to histology codes 9060–9085. Data were analyzed using SAS/STAT release 8.2, SEER*Stat version 5.2, and SPSS version 13.0 software. A total of 1,467 cases of malignant pineal germ-cell tumors were identified: 1,159 from NCDB, 196 from SEER, and 112 from CBTRUS. All three databases showed a male predominance for pineal germ-cell tumors (>90%), and >72% of patients were Caucasian. The peak number of cases occurred in the 10- to 14-year age group in the CBTRUS data and in the 15- to 19-year age group in the SEER and NCDB data, and declined significantly thereafter. The majority of tumors (73%–86%) were germinomas,

and patients with germinomas had the highest survival rate (>79% at 5 years). Most patients were treated with surgical resection and radiation therapy or with radiation therapy alone. The number of patients included in this study exceeds that of any study published to date. The proportions of malignant pineal germ-cell tumors and intracranial germ-cell tumors are in range with previous studies. Survival rates for malignant pineal germ-cell tumors are lower than results from recent treatment trials for intracranial germ-cell tumors, and patients that received radiation therapy in the treatment plan either with surgery or alone survived the longest. *Neuro-Oncology* 10, 121–130, 2008 (Posted to *Neuro-Oncology* [serial online], Doc. D07-00041, February 20, 2008. URL <http://neuro-oncology.dukejournals.org>; DOI: 10.1215/15228517-2007-054)

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Data from epidemiologic studies of pineal tumors are limited and lack the collective information from the centralized brain tumor registries. Estimates on the proportion of pineal tumors vary from 3% to 5% of intracranial tumors in children and from 0.4% to 1% of intracranial tumors in adults.^{1–5} These estimates have been calculated by pooling data from studies performed in institutional settings or studies having a small sample size. With a majority (50%–70%) of these pineal region tumors being of germ-cell origin, and with germ-cell tumors being the most curable primary intra-

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cranial malignancy, updated incidence and survival data for the general population are needed.⁴⁻⁷ Information from large databases can reduce the biases associated with institutional studies and provide descriptive data relevant to the general population.

Germ cells are considered to be totipotent cells, able to differentiate into any cell type.⁸⁻¹⁰ These primordial cells appear in the yolk sac of the embryo during the third to fourth week of gestation.¹¹ Although their normal destination (via the dorsal mesentery of the hindgut) is the ovaries or testes, it is believed that some germ cells migrate to other locations within the developing embryo.^{11,12} The cause of this migration remains unknown, but the cells come to rest mainly in midline sites, including the mediastinum, sacrococcygeal region, and the third ventricle.^{5,12,13} Most pineal germ-cell tumors are thought to be due to the midline location of the pineal gland near the third ventricle, but the histogenesis is unknown.⁵

The pineal body is a cone-shaped structure that overlies the midbrain and contains glial cells and parenchymal cells (i.e., pineocytes), along with nerve fibers.^{14,15} The pineal body has fascinated neuroendocrinologists as the site of melatonin production, but the pineal region has also interested neurosurgeons and oncologists due to the high prevalence of primary germ-cell tumors.¹⁶ Primary pineal tumors can be divided into three groups: (1) tumors of germ-cell origin, (2) tumors of pineal parenchymal origin (e.g., pineocytoma, pineoblastoma), and (3) tumors of tissues supporting or adjacent to the pineal gland (e.g., meningioma, glioma).¹⁵ Metastatic tumors, vascular lesions, and infections or inflammatory processes can also occur in this area. Pineal germ-cell tumors may be benign but are predominantly malignant. The WHO classification of tumors of the nervous system lists multiple histologies for germ-cell tumors: germinoma, teratoma, mature teratoma, immature teratoma, teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor, and combinations of the above (i.e., mixed germ-cell tumors).¹⁵ It is common to have a mixed histologic composition, but most germinomas are histologically pure.

The purpose of the present study was to provide a comprehensive overview of malignant pineal germ-cell tumors by collecting data from a large number of patients, obtained using three different databases: the Surveillance, Epidemiology, and End Results (SEER) database; the Central Brain Tumor Registry of the United States (CBTRUS); and the National Cancer Data Base (NCDB). Our report of 1,467 cases of malignant pineal germ-cell tumors provides current data on descriptive statistics, treatment patterns, and survival estimates for these tumors.

Methods

Three databases were used to obtain information on patients with primary malignant pineal germ-cell tumors. The SEER program is sponsored by the National Cancer Institute and collects population-based incidence and

survival data on all primary malignant cancers.¹⁷ Five states (CT, HI, IA, NM, UT) and four metropolitan areas (Atlanta, Detroit, San Francisco–Oakland, Seattle–Puget Sound) were included, representing approximately 14% of the U.S. population.¹⁸ The SEER April 2004 public-use data were used to analyze information on all primary malignant pineal germ-cell tumors reported between 1973 and 2001.¹⁷ CBTRUS compiles population-based incidence data on all primary brain and CNS tumors, regardless of biologic behavior, and represents approximately 30% of the U.S. population.³ Information was provided to CBTRUS from 15 state cancer registries (AZ, CO, CT, DE, ID, ME, MA, MN, MT, NM, NY, NC, TX, UT, VA). For this study, data from CBTRUS were compiled for the years 1997–2001. NCDB is a hospital-based tumor registry providing data and follow-up information on all primary malignant tumors (and voluntarily on benign tumors for the years included in this review) from institutions approved by the Commission on Cancer of the American College of Surgeons, estimated to reflect approximately 70% of all cancer patients in the United States after the year 1996.¹⁹ NCDB data from 1985–2003 on patients with malignant pineal germ-cell tumors were included in this study. The three databases are not mutually exclusive, and case overlap among databases exists. Cases diagnosed at autopsy were excluded from all three data sets.

The set of “all primary malignant brain tumors” was defined by using the International Classification of Diseases for Oncology, third edition (ICD-O-3), site codes of C70.0–C72.9 and C75.1–C75.3, and a behavior code of 3 (i.e., malignant).²⁰ Pineal tumors were identified using the ICD-O-3 site code of C75.3, and pineal germ-cell tumors were further selected by using ICD-O-3 histology codes 9060–9085.²⁰ The identified cases were grouped into the following histologic categories: germinoma (9060, 9061, 9064, 9065), teratoma (9080, 9082, 9084), mixed germ-cell tumor (9081, 9085), and “other” (embryonal carcinoma [9070], endodermal sinus [9071]).

Frequencies and means for variables from each of the three data sets were obtained using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, USA), and SAS/STAT, release 8.2 (SAS Institute, Inc., Cary, NC, USA). Incidence rates, age adjusted to the 2000 U.S. standard population, were estimated for the CBTRUS data using SAS/STAT, release 8.2, and for the SEER data using SEER*Stat version 5.2.¹⁷ Survival rates were estimated from the SEER data set (for those diagnosed between 1973 and 2001, except for surgery, which was restricted to those diagnosed between 1983 and 1997) and from NCDB (for those diagnosed between 1985 and 1998). Relative survival was defined as the observed probability of survival adjusted for the expected survival rate of the U.S. population for that age, sex, and race. Survival time was calculated from the date of diagnosis to the date of death or last contact. Patients who were alive were censored at the date of last contact. Survival rates were not estimated for categories with fewer than 10 cases. SEER*Stat version 5.2, available on the SEER public-use CD-ROM, was utilized to obtain 2- and 5-year relative

survival rates for the SEER data.¹⁷ Survival rates were estimated in 1-year intervals for a period of 5 years using the life-table method to properly account for right censoring. The Kaplan-Meier product-limit method was used to estimate observed survival in 1-year intervals for a period of 5 years, and comparisons were made using the log-rank test.

Evaluation of treatment was limited to cases identified from SEER (surgery and radiation therapy) and NCDB (surgery, radiation therapy, and chemotherapy). Hormonal and immunotherapy treatment variables were not considered in the analyses for either data set. The variable for radiation therapy was categorized as “yes” (those patients who received any form of radiation therapy) or “no” (patients who received no radiation therapy). The variable for surgery was defined as “yes” (patients receiving any type of definitive or cancer-directed surgery) or “no” (patients who did not undergo definitive or cancer-directed surgery or who received exploratory or biopsy surgery only). Similarly, the variable for chemotherapy was categorized as “yes” (those patients who received any form of chemotherapy) or “no” (patients who received no chemotherapy). Information on chemotherapy was not available in the SEER data set. To investigate the role of chemotherapy on survival in different time periods, 5-year survival estimates were compared between those who did and those who did not receive chemotherapy separately for subjects diagnosed between 1985–1990 and 1994–1998. To further evaluate the effects of definitive (or cancer-directed) surgery and radiation therapy on survival rates (chemotherapy was not included, as the additional stratification resulted in multiple cells with insufficient numbers of cases), all cases from NCDB were categorized into one of four surgery/radiation therapy combinations: (1) no definitive surgery and no radiation therapy, (2) definitive surgery but no radiation therapy, (3) radiation therapy but no definitive surgery, and (4) both definitive surgery and radiation therapy.

Results

A total of 44,251 cases of malignant brain and CNS tumors were identified between 1973 and 2001 using the SEER database. Of these, 335 tumors (0.76%) were located in the pineal region. Of all tumors of germ-cell origin, 370 germ-cell tumors were reported to have occurred in the brain and CNS (2.04%), and 196 (53.0%) of these were located specifically in the pineal region, of which 90.8% were microscopically confirmed. Using CBTRUS data from 1997 to 2001, 112 of 284 (39.4%) brain and CNS germ-cell tumors were located in the pineal region. Classification of malignant germ-cell tumors to areas outside of the pineal region included a group of brain and nervous system tumors “not otherwise specified” (60/284, 21.2%), as well as cerebrum, frontal, temporal, and parietal lobes (32/284, 11.3%); ventricle (20/284, 7.0%); posterior fossa (8/284, 2.8%); pituitary region (31/284, 10.9%); spinal cord and optic nerve (6/284, 2.1%); and overlapping lesions of the brain (15/284, 5.3%). The proportion of all primary malig-

nant intracranial brain tumors that were malignant pineal germ-cell tumors was 2.2% for children through 19 years of age and 0.18% for adults 20 or more years of age. Of 2,172 malignant pineal tumors ascertained from NCDB data for the years 1985 to 2003, 1,159 (53.4%) were classified as germ-cell tumors. Forty-eight percent (1,159/2,412) of malignant brain and CNS germ-cell tumors were located in the pineal region.

All three databases showed a male predominance for malignant pineal germ-cell tumors, with the male:female ratios ranging from 14.3:1 to 21.4:1 (Table 1). The majority of the patients (>72% in each database) were Caucasian. Overall, germ-cell tumors accounted for 53.0% of all malignant tumor histologies in the pineal region in the SEER database, with germinomas making up the greatest proportion of pineal region germ-cell tumors (73.0%; Table 1). Similarly, in the CBTRUS and NCDB data sets, germinomas comprised the greatest proportion of pineal germ-cell cases (85.7% and 80.9%, respectively). The relative frequencies of mixed germ-cell tumors were similar across the databases, while the relative frequencies of the teratomas and the “other” germ-cell tumors were lower in the CBTRUS data set. Collectively, the mixed germ-cell tumors, teratomas, and “other” germ-cell tumors accounted for only about 20% of pineal germ-cell tumors.

The age at the time of diagnosis of a malignant pineal germ-cell tumor ranged from 0–86 years (Table 1). The highest frequency of new cases occurred in the second decade for all databases (Fig. 1). The tumor frequency was found to progressively decrease with increasing age, with few cases being diagnosed after age 30. In the SEER database, mixed germ-cell tumors had the lowest mean age at onset (14.3 years), and germinomas were diagnosed at a mean age of 19.2 years. In both CBTRUS and NCDB data, teratomas had the lowest mean age at diagnosis (10.5 years and 11.6 years, respectively). Germinomas also had the latest mean age at diagnosis (20.2 years) in the NCDB database, similar to the SEER data, whereas “other” germ-cell tumors were diagnosed at a later mean age (28.5 years) in the CBTRUS data. Confidence intervals for mean age at diagnosis did not overlap between the mixed germ-cell tumors and germinomas in either the NCDB or SEER data (Table 1). Teratomas also had a significantly younger age at onset than either the mixed germ-cell tumors or germinomas in the NCDB data. Confidence intervals (CIs) for the mean age at diagnosis for the CBTRUS data and for the “other” tumor histologies were wide due to smaller numbers of cases. Median age at diagnosis was similar to the mean age at diagnosis for all histologies in the NCDB and CBTRUS data (Table 1). However, in the SEER data, the median age at diagnosis of germinoma (11 years) was much lower than the mean age at diagnosis (19.2 years).

The incidence of malignant pineal germ-cell tumors was estimated to be 0.025/100,000 person-years using the CBTRUS data, with a higher rate in males (0.048/100,000) than in females (0.002/100,000). Incidence rates were also higher for males (0.050/100,000) than females (0.004/100,000) in the SEER data. Incidence in Caucasians and African Americans was similar

Table 1. Demographic characteristics of malignant pineal germ-cell tumors from three U.S. databases: SEER, 1973–2001; CBTRUS, 1997–2001; and NCDB, 1985–2003 [*n* (%)]

	SEER	CBTRUS	NCDB
Total cases	196	112	1,159
Gender			
Male	184 (93.9)	107 (95.5)	1,083 (93.4)
Male:female ratio	15.3:1	21.4:1	14.3:1
Race			
Caucasian	142 (72.5)	95 (84.8)	933 (80.5)
African American	18 (9.2)	10 (8.9)	103 (8.9)
Other/unknown	36 (18.3)	7 (6.3)	123 (10.6)
Histology			
Germinoma	143 (73.0)	96 (85.7)	938 (80.9)
Mixed germ cell	26 (13.3)	12 (10.7)	122 (10.5)
Teratoma	18 (9.2)	N/A	62 (5.3)
Other	9 (4.6)	N/A	37 (3.2)
Age group			
<20 years	134 (68.4)	66 (58.9)	714 (61.6)
≥20 years	62 (31.6)	46 (41.1)	443 (38.2)
Mean age at diagnosis			
Germinoma	19.2 years (95% CI, 17.7–20.7)	20.5 years (95% CI, 18.2–22.8)	20.2 years (95% CI, 19.6–20.8)
Mixed germ cell	14.3 years (95% CI, 12.8–15.8)	15.1 years (95% CI, 11.2–19.0)	16.6 years (95% CI, 15.0–18.1)
Teratoma	16.2 years (95% CI, 9.4–23.0)	10.5 years (95% CI, 3.6–17.4)	11.6 years (95% CI, 9.7–13.5)
Other	17.9 years (95% CI, 14.8–21.0)	28.5 years (95% CI, 11.8–45.2)	16.0 years (95% CI, 13.6–18.3)
Median (min–max) age at diagnosis			
Germinoma	11 years (5–63 years)	18 years (3–67 years)	18 years (1–86 years)
Mixed germ cell	14 years (7–23 years)	13 years (7–34 years)	15 years (6–83 years)
Teratoma	13 years (5–69 years)	10 years (7–14 years)	11 years (0–51 years)
Other	20 years (8–23 years)	28 years (20–37 years)	15 years (1–42 years)
Vital status			
Alive	138 (70.4)	— ^a	975 (84.1)
Deceased	58 (29.6)	— ^a	184 (15.9)
Radiation therapy			
No	26 (13.3)	— ^a	244 (21.1)
Yes	164 (83.7)	— ^a	865 (74.6)
Unknown	6 (3.1)	— ^a	50 (4.3)
Surgery			
No	77 (39.3)	— ^a	620 (53.5)
Yes	82 (41.8)	— ^a	525 (45.3)
Unknown	37 (18.9)	— ^a	14 (1.2)
Chemotherapy			
No	— ^a	— ^a	672 (58.0)
Yes	— ^a	— ^a	467 (40.3)
Unknown	— ^a	— ^a	20 (1.8)
Surgery/radiation combination			
Surgery/radiation	82 (35.7)	— ^a	375 (32.4)
Surgery only	15 (6.5)	— ^a	123 (10.6)
Radiation only	45 (19.6)	— ^a	482 (41.6)
Neither	8 (3.8)	— ^a	117 (10.1)
Unknown	46 (23.5)	— ^a	62 (5.3)

Abbreviation: N/A, unable to calculate due to small sample size.

^aThese data were not collected.

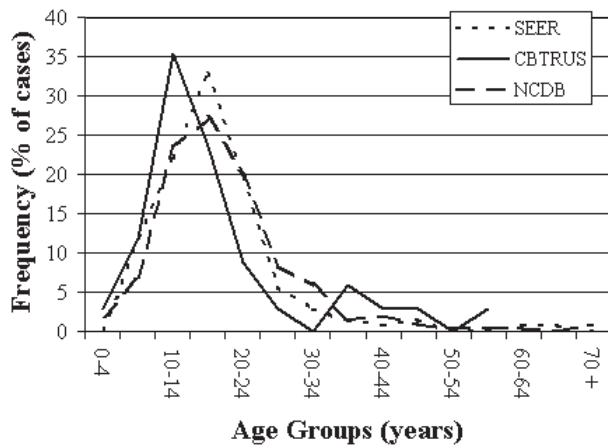


Fig. 1. Age at diagnosis of a malignant pineal germ-cell tumor, by database: CBTRUS (1997–2001), SEER (1973–2001), and NCDB (1985–2003).

(0.025/100,000 and 0.020/100,000, respectively). In SEER, germinomas showed the highest incidence rate of 0.020/100,000, whereas the incidence of mixed germ-cell tumors was 0.004/100,000. Teratomas and “other” germ-cell tumors had incidence rates of 0.002/100,000 and 0.001/100,000, respectively (Fig. 2).

No evidence for an increase in pineal germ-cell tumors over time from 1985 to 1999 (average annual percent change [AAPC] = 0.04; 95% confidence interval [95% CI], −7.04 to 7.16), as well as no sharp changes in incidence over time, was found for a subset of the CBTRUS data (from five collaborating registries). In contrast, over the time period 1973–2001, the age-adjusted incidence of malignant pineal germ-cell tumors in the SEER data set increased significantly (AAPC = 3.43; 95% CI, 1.60–5.29), although no sharp changes in incidence were identified.

Two- and five-year relative survival rates were estimated using the SEER data (Table 2). For patients with any malignant pineal germ-cell tumor, estimates were 79.4% (95% CI, 67.5%–91.3%) for 2-year relative survival and 73.7% (95% CI, 60.2%–87.3%) for 5-year relative survival. Two- and five-year relative survival ranged from a low of 47.1% and 33.8% (although the

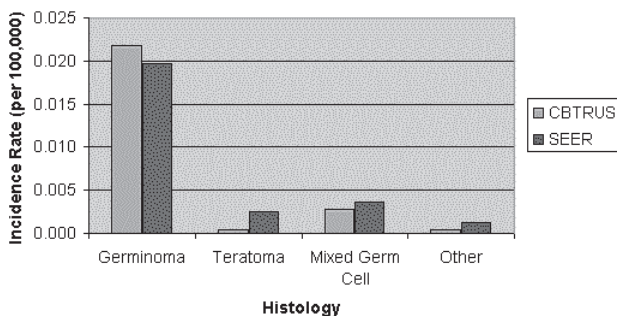


Fig. 2. Incidence rates for the different histologic categories of malignant pineal germ-cell tumors using CBTRUS (1997–2001) and SEER (1973–2001) data.

small number of cases [$n = 17$] made for highly unstable rates, 95% CI, 0%–94.8%), respectively, for those with teratomas to a high of 85.7% (95% CI, 73.3%–98.2%) and 79.5% (95% CI, 64.4%–94.7%), respectively, for those with germinomas ($n = 142$). Patients with mixed germ-cell tumors ($n = 26$) had a relative survival of 83.8% (95% CI, 52.0–100%) at 2 and 5 years. Because germinomas were the largest histologic subgroup, the survival rates for these tumors were primarily responsible for the higher survival rates in the overall survival estimates. Comparison of the survival curves demonstrated significantly better survival for germinomas and mixed germ-cell tumors than for teratomas ($p < 0.001$). There were no significant differences in 2- or 5-year survival by age group (<20 vs. >20 years), race, or gender.

NCDB data were also used to estimate 2- and 5-year relative survival rates for malignant pineal germ-cell tumors (Table 2). Overall survival was 88.4% (95% CI, 86.1%–90.7%) at 2 years and 82.5% (95% CI, 79.7%–85.4%) at 5 years. Rates for 2- and 5-year relative survival for NCDB cases with germinomas were slightly higher than those found in the SEER database (92.0% [95% CI, 89.9%–94.2%] and 86.0% [95% CI, 83.1%–89.0%], respectively). In contrast to SEER, NCDB patients with a mixed germ-cell tumor histology had the worst 2- and 5-year relative survival rates (68.9% [95% CI, 57.9%–80.0%] and 66.2% [95% CI, 54.7%–77.6%], respectively). Survival for those with teratomas was intermediate to the other two histology groupings in NCDB (2-year survival, 84.8% [95% CI, 74.3%–95.4%]; 5-year survival, 74.8% [95% CI, 61.5%–88.0%]). Log-rank comparisons of the survival curves for the histology groupings demonstrated that those with germinomas had significantly better survival than those with mixed germ-cell tumors ($p < 0.001$) and borderline significantly better survival than those with teratomas ($p = 0.06$).

Further subgroup analysis of NCDB data was performed with respect to tumor histology and treatment (Table 3). Definitive surgery was performed on the majority of teratomas (51/62 cases, 82.3%) and mixed germ-cell tumors (90/122 cases, 73.8%). For germinomas, however, the majority received no definitive surgery (562/934 cases, 60.2%). Table 3 also shows the proportion of nonsurgical cases that received radiation therapy, by histology. For germinomas, when definitive surgery was not performed, most received radiation therapy (445/562 cases, 79.2%). Similarly, most mixed germ-cell tumor (62.5%) and teratoma (data not shown due to small sample size) cases received radiation therapy when they did not receive definitive surgery, but the frequency was lower than for germinomas.

Five-year relative survival for those diagnosed with any pineal germ-cell tumor in the SEER database and undergoing radiation therapy was 78.2% (95% CI, 71.3%–85.1%) compared to 51.0% (95% CI, 29.3%–72.7%) for those who did not have any radiation therapy (Table 2). Five-year relative survival was statistically significantly better for patients with germinomas who underwent radiation therapy compared to

Table 2. Two- and five-year relative survival estimates [% (95% confidence interval)] for malignant pineal germ-cell tumors from two U.S. databases: SEER, 1973–2001; and NCDB, 1985–1998

	SEER		NCDB	
	2-Year Survival	5-Year Survival	2-Year Survival	5-Year Survival
Histology				
All pineal germ-cell tumors	79.4 (67.5–91.3)	73.7 (60.2–87.3)	88.4 (86.1–90.7)	82.5 (79.7–85.4)
Germinoma	85.7 (73.3–98.2)	79.5 (64.4–94.7)	92.0 (89.9–94.2)	86.0 (83.1–89.0)
Mixed germ-cell tumor	83.8 (52.0–100)	83.8 (52.0–100)	68.9 (57.9–80.0)	66.2 (54.7–77.6)
Teratoma	47.1 (0–94.8)	33.8 (0–94.8)	84.8 (74.3–95.4)	74.8 (61.5–88.0)
Other	N/A	N/A	N/A	N/A
Radiation therapy				
All pineal germ-cell tumors				
Yes	82.2 (76.1–88.4)	78.2 (71.3–85.1)	90.8 (88.4–93.2)	85.3 (82.2–88.3)
No	66.1 (46.3–85.8)	51.0 (29.3–72.7)	82.2 (76.1–88.2)	75.0 (67.7–82.3)
Germinomas only				
Yes	87.9 (84.9–90.9)	83.6 (80.1–87.1)	94.2 (92.1–96.3)	88.2 (85.2–91.2)
No	75.1 (59.8–90.4)	45.3 (26.4–64.2)	85.5 (78.8–92.2)	80.4 (72.3–88.6)
Definitive surgery^a				
All pineal germ-cell tumors				
Yes	80.7 (71.9–89.4)	78.4 (69.2–87.7)	87.8 (84.3–91.2)	81.7 (77.5–85.9)
No	75.6 (65.7–85.4)	66.7 (55.7–77.5)	89.7 (86.7–92.8)	83.8 (79.9–87.7)
Germinomas only				
Yes	87.2 (82.2–92.2)	87.2 (82.2–92.2)	93.0 (89.8–96.3)	87.5 (83.1–91.9)
No	85.0 (80.6–89.4)	74.7 (69.2–80.2)	92.3 (89.4–95.1)	85.8 (81.9–89.6)
Chemotherapy				
All pineal germ-cell tumors				
Yes	— ^b	— ^b	82.6 (77.8–87.3)	76.7 (71.2–82.2)
No	— ^b	— ^b	92.0 (89.5–94.4)	85.9 (82.7–89.2)
Germinomas only				
Yes	— ^b	— ^b	89.8 (85.0–94.5)	83.5 (77.4–89.6)
No	— ^b	— ^b	93.4 (91.0–95.8)	87.4 (84.1–90.7)

Abbreviation: N/A, unable to calculate due to small sample size.

^aSurvival was estimated for those diagnosed between 1983 and 1997 for SEER and between 1985 and 1998 for NCDB.^bThese data were not collected.**Table 3.** NCDB data on extent of surgical resection and on radiation treatment of nonsurgery cases by histology group [*n* (%)]

	Germinoma	Mixed Germ-Cell Tumor	Teratoma
Total	934	122	62
Surgical procedure of primary site^a			
None (includes biopsy only)	562 (60.2)	32 (26.2)	11 (17.7)
Local or partial removal	208 (22.3)	46 (37.7)	30 (48.4)
Total surgical removal of primary site/radical surgery	50 (5.4)	25 (20.5)	10 (16.1)
Surgery NOS	105 (11.2)	19 (15.6)	11 (17.7)
Radiation treatment in nonsurgical cases^a			
No	100/562 (17.8)	11/32 (34.4)	N/A
Yes	445/562 (79.2)	20/32 (62.5)	N/A

Abbreviations: NOS, not otherwise specified; N/A, unable to calculate due to small sample size.

^aCounts may not add to total number because some subgroups are not presented here.

those who did not (83.6% vs. 45.3%). For those with any pineal germ-cell tumor who had surgery, 5-year relative survival was 78.4% (95% CI, 69.2%–87.7%), compared to 66.7% for those who did not have surgery (95% CI, 55.7%–77.5%). For germinoma patients who underwent surgery, 5-year relative survival was statistically significantly better than for those who did not undergo surgery (87.2% vs. 74.7%). Comparison of the survival curves indicated that those with any pineal germ-cell tumor undergoing radiation therapy in the SEER data set had significantly better survival than did those who did not undergo radiation therapy ($p = 0.03$), whereas survival among those with any pineal germ-cell tumor who had surgery did not differ from those who did not have surgery ($p = 0.49$). Information on chemotherapy was not available in the SEER data set.

Similar to the SEER results and regardless of other treatments, patients with any pineal germ-cell tumor in the NCDB undergoing radiation therapy also had better 5-year relative survival than did those who did not receive radiation therapy (85.3% [95% CI, 82.2%–88.3%] vs. 75.0% [95% CI, 67.7%–82.3%], respectively; p value for log-rank comparison of the survival curves < 0.0001), whereas 5-year relative survival did not differ between those with any pineal germ-cell tumor who received surgery and those who did not (81.7% [95% CI, 77.5%–85.9%] vs. 83.8% [95% CI, 79.9%–87.7%], respectively; Table 2). Pineal germ-cell cases in NCDB that received chemotherapy, disregarding other treatments, had lower 5-year survival than those who did not receive chemotherapy (76.7% [95% CI, 71.2%–82.2%] vs. 85.9% [95% CI, 82.7%–89.2%], respectively). When data were analyzed separately by time period, those diagnosed between 1985 and 1990 and receiving chemotherapy had lower 5-year observed survival than those who did not receive chemotherapy (61.1% vs. 84.2%, respectively; p value for log-rank comparison of the survival curves = 0.001), whereas there was no difference in the survival curves between those diagnosed between 1994 and 1998 who received chemotherapy and those who did not (5-year observed survival 80.6% vs. 87.3%, respectively; p value for log-rank comparison of the survival curves = 0.15). Similar, but slightly higher, 5-year relative survival rates were found for those with germinomas with and without chemotherapy (83.5% vs. 87.4%, respectively).

Although the number of SEER cases was too small to categorize by both radiation therapy and surgery, that information was available for a large number of cases from the NCDB data set ($n = 780$; data set for 1985–1998). This allowed comparison of survival over the first 5 years after diagnosis, based on the four treatment combinations (Table 1, Fig. 3a). Five-year relative survival was highest in patients with any pineal germ-cell tumor who underwent radiation treatment but did not have surgery (85.9%; 95% CI, 81.8%–90.0%). Patients with any germ-cell tumor who underwent both surgery and radiation therapy had a 5-year survival estimate of 84.5% (95% CI, 79.8%–89.2%), whereas those who had neither surgery nor radiation treatment had a similar 5-year survival rate of 79.9% (95% CI,

69.8%–89.9%). Reasons for the lack of treatment by either of these methods are unknown but may be related to clinical characteristics, such as anatomic features of the tumor, or patient choice. The lowest 5-year survival rates (71.6%) were experienced by those with any pineal germ-cell tumor who underwent surgery only (95% CI, 61.3%–81.8%). The survival curves for those who had both surgery and radiation therapy and for those who had radiation only were statistically significantly different from those patients who had surgery but no radiation treatment ($p = 0.008$ and $p = 0.002$, respectively), with the slope of the curve for those who had surgery but no radiation therapy declining more rapidly in the first 12 months after diagnosis.

For those patients diagnosed with germinoma, the results were similar to the results for those with any pineal germ-cell tumor (Fig. 3b). The highest 5-year relative survival rates were observed in those who received radiation and surgery (89.7%; 95% CI, 85.1%–94.4%) and in those who received radiation treatment alone (87.2%; 95% CI, 83.1%–91.3%). Germinoma patients with no radiation or surgical treatment had 5-year rela-

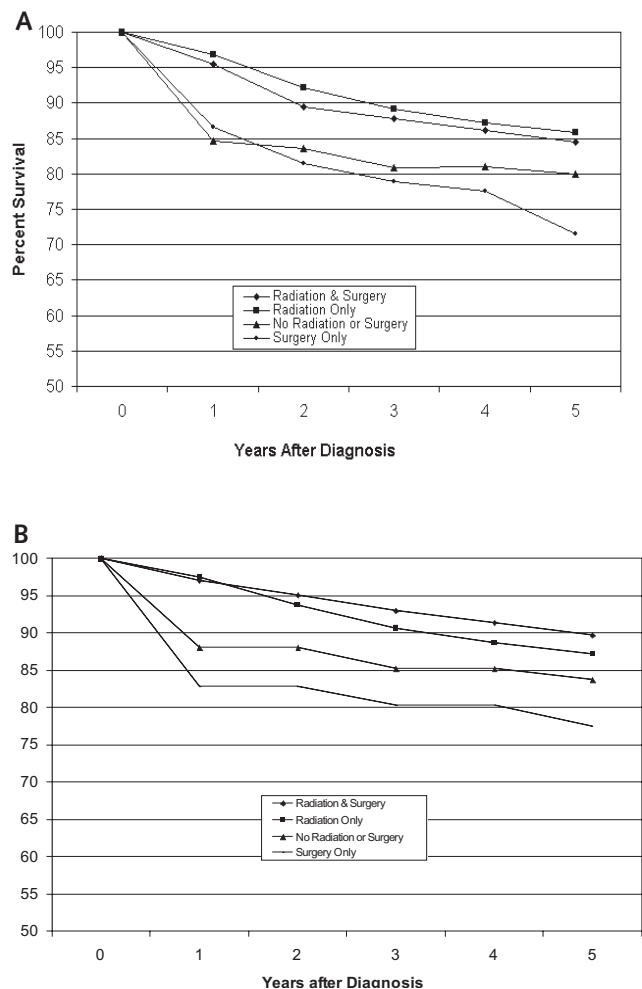


Fig. 3. Survival for all pineal germ-cell tumors (A) and germinomas (B) according to treatment category using NCDB data, 1985–1998.

tive survival of 83.8% (95% CI, 73.6%–94.1%), while those with surgery only had the poorest 5-year relative survival (77.5%; 95% CI, 64.5%–90.5%). Comparison of the survival curves for those with germinoma showed that those who received surgery only had statistically significantly poorer survival than those who received radiation treatment alone or in combination with surgery ($p = 0.03$ and $p = 0.01$, respectively).

Discussion

Pineal germ-cell tumors are rare, often striking in a very young patient population. Because there is a high potential for cure, it is important to review the nationwide outcome data to ensure all cases receive the best possible treatment. This study details the largest published series of patients with malignant pineal germ-cell tumors with a broad U.S. demographic. Most previous reports have been case reviews from single institutions, which are subject to potential referral biases by the systematic inclusion or exclusion of patients with certain characteristics, especially those who are in a particular age (e.g., pediatric) or demographic group or treated in a defined manner (e.g., biopsy and radiation therapy).^{1,2,4–6,11,22, 23} Although this information can have value on a case-by-case or institutional basis (e.g., in publicizing a particular treatment option), such studies may not provide information representative of the general population, especially for a disease as rare as pineal region tumors.

For the present study, three established cancer databases were utilized, with each providing distinct contributions. These databases allow collection of a larger and more diverse group of cases. SEER provides population-based incidence and survival data for all primary malignant tumors in the United States and has set the gold standard for cancer data collection. CBTRUS is a population-based data resource that includes brain and CNS tumors of all behaviors (i.e., benign and malignant) from 15 U.S. regions from 1997 to 2001. NCDB is a hospital-based database that collects information from hospitals approved by the Commission on Cancer of the American College of Surgeons.¹⁹ Although NCDB's data collection does not allow incidence rates to be estimated, it does provide the most information about descriptions of tumors at diagnosis, treatment information, and survival outcome data on a large proportion (~70%) of U.S. cancer patients diagnosed after 1996. Although population-based registries, such as SEER and CBTRUS, are useful for estimating incidence, tumor characteristics, or survival in all patients diagnosed with cancer in given regions, the broad coverage and large numbers of cases included in the hospital-based NCDB data approximate the population-based registries for descriptive statistics and survival.²⁴ Although there is a small degree of case overlap among registries, each database was analyzed individually, and data were not combined. Using the data obtained from these three databases, a more generalizable statistical description of malignant pineal region germ-cell tumors can be obtained.

In our review, pineal region tumors accounted for

<0.8% of brain and CNS tumors (falling within the previously published range of 0.4%–1%).^{3,5,6} Of those, 54.0% were germ-cell tumors. Intracranial germ-cell tumors made up only 2.04% of all germ-cell tumors (including gonadal and mediastinal). Of the intracranial germ-cell tumors, nearly half were located in the pineal region. Much of the discordance in the frequencies and rates between the three databases is likely due to smaller numbers of cases in CBTRUS, resulting in wider confidence intervals, although the overall conclusions are similar across the three databases. Results of this analysis confirmed that such tumors affect predominantly male patients (15:1), although previously published estimates of the male:female ratio were much lower (4:1), with a peak incidence of 10–19 years of age.^{1,2,5,25} Teratomas presented at an earlier age than did other tumors. The most common histology seen is germinoma (73%–86%), which was more frequent than observed in previous studies (58%–65% of intracranial germ-cell tumors).^{2,5,22} Overall, about two-thirds of the patients survived 5 years, with germinoma patients surviving longer than those with other tumor types. Furthermore, analysis of the databases revealed that patients were usually treated with surgery and radiation or with radiation alone.

Tumor registry data are important for looking at overall survival and in determining, in general, what types of therapeutic options have been used in clinical management and their expected outcomes. Our analysis of treatment and survival from SEER and NCDB demonstrate that radiation therapy either alone or with surgery is the most efficacious therapy for malignant pineal germ-cell tumors. This reaffirms the survival benefit observed with radiation therapy^{26,27} and is in keeping with the most current prospective treatment trials of intracranial germ-cell tumors that incorporate radiation therapy in sequence with chemotherapy.^{7,28,29} Although current registry data do not provide information on the dose, volume, or treatment planning, the field is evolving as germ-cell tumors are uniquely sensitive to radiation therapy. This includes limiting radiation doses in pediatric and adolescent patients and new treatment planning such as dynamic adaptive radiation therapy.³⁰ This therapy consists of constant monitoring of target tumor volume with compensation for changes, which is ideal for radiation-responsive tumors with nearby vital structures (e.g., the optic chiasm for pineal tumors).

Our analysis indicates that chemotherapy or surgery alone does not improve survival. Overall analysis demonstrates lower 5-year survival for subjects undergoing chemotherapy than for those who do not. Two earlier prospective trials from 1989–1997 evaluated platinum-based therapy without radiation therapy for primary treatment of intracranial germ-cell tumors.^{31,32} Both reported significant toxicity or an unacceptably high rate of relapse. Our data likely reflect changes in chemotherapy use over time. Subgroup analysis of 5-year survival data for patients diagnosed most recently (1994–1998) did not detect a difference between those who received chemotherapy and those who did not. It is also possible that chemotherapy was reserved for patients with refrac-

tory or advanced disease, and/or poor performance status, but clearly chemotherapy alone is not the standard.

Survival rates for germinomas were similar in the SEER and NCDB data. A difference, however, was seen between databases for mixed germ-cell tumors and teratomas. Although the teratoma survival rate was lower and the mixed germ-cell tumor survival rate was higher in the SEER data set, the confidence intervals around the survival rates were very wide due to small numbers of cases. In addition, small numbers prevent detailed analyses of treatment options from SEER for the young patient population. However, we were able to analyze clinical management from the NCDB population. The NCDB mixed germ-cell and teratoma tumor patients were treated predominantly by surgical excision. For those mixed germ-cell cases that were not surgically treated, radiation therapy was received in only 62% of the cases, while almost three-quarters of teratoma cases that were not surgically treated (data not shown) received radiation therapy. Given the limitations of our analysis, the results provoke questions as to how aggressive treatment for these rare subtypes (teratoma and mixed germ-cell tumor) should be to ensure the best survival.

The 2- and 5-year survival rates for patients with malignant germ-cell tumors found in this study are somewhat lower than in recently published treatment studies.^{7,28,29} This could be due to the inherent academic bias in studying a rare disease in limited institutional settings with defined enrollment guidelines, or because the time period for our data did not reflect the current improved therapy of sequential treatment with chemoradiotherapy, or that the therapy had not yet been widely adopted. Regardless, our data may more accurately reflect the true course of disease and its treatment. Future studies may reveal whether one or more of these factors are involved. Our survival curves based on treatment modality illustrate the benefit of radiation therapy and that it is superior to either surgery or chemotherapy. This is in contrast to gonadal germ-cell tumors, where surgical excision is often curative for early-stage non-seminoma germ-cell tumors, and chemotherapy is highly curative for patients with advanced disease.^{33,34} These

treatment differences may reflect the differences in tumor location more than the differences in tumor biology.³⁵ Although pineal germ-cell tumors have among the highest cure rates of primary malignant tumors in the brain, curative therapy in the brain is more difficult than for noncranial germ-cell tumors and requires an interdisciplinary approach.³⁶

The use of registries is essential for obtaining generalizable epidemiologic information on tumors, because all cases are included regardless of the method of diagnosis or treatment. We recognize the limitations of registry information, because data collected over a long time period may not be comparable due to changes in coding, classification, diagnosis, and treatment. This is especially true for the SEER data set, which extends as far back as 1973, predating current imaging modalities such as MRI and CT scans. The collection of data in our study occurred largely prior to publication of the widely used WHO classification of tumors of the nervous system in 2000.¹⁵ However, the classification of pineal tumors has remained largely unchanged, based on the Berger neurologic pathology manuals that predated the WHO publication, and is not likely to greatly affect the classification system in our study.^{21,37}

In summary, our use of multiple cancer registries on this rare tumor provides a larger sample size than previously published and allows a comprehensive overview of statistics, treatment patterns, and survival. Our analysis revealed greater male incidence in malignant pineal germ-cell tumors and reaffirms the survival benefit seen with radiation therapy.

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